IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Frank A. Skraly		
Serial No.:	10/661,939	Art Unit:	1652
Filed:	September 12, 2003	Examiner:	Iqbal Hussain Chowdhury
For:	*POLYHYDROXYALKANOATE PRODUCTION BY COENZYME A-DEPENDENT ALDEHYDE DEHYDROGENASE PATHWAYS*		

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Sir:

This is a Reply Brief to the Examiner's Answer mailed on January 17, 2008. A Notice of Appeal was filed on April 27, 2007, with a two months extension of time. Submitted with this Reply Brief is a Request for Oral Hearing. The Commissioner is hereby authorized to charge $1,030.00, the fee for a Request for Oral Hearing for a large entity to Deposit Account No. 50-3129.

It is believed that no further fee is required with this submission. However, should a fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues presented on appeal are:

(1) whether claims 16-23 meet the written description requirement of 35 U.S.C. § 112, first paragraph.

(2) whether claims 16-23 are enabled as required by 35 U.S.C. § 112, first paragraph.

(7) ARGUMENTS

Appellants affirm all of the arguments made in the Appeal Brief.

(i) The claimed organisms

Polyhydroxyalkanoates (PHAs) are natural, thermoplastic polyesters and can be processed by traditional polymer techniques for use in an enormous variety of applications, including consumer packaging, disposable diaper linings and garbage bags, food and medical products. The enzymes in the polyhydroxybutyrate (PHB) biosynthetic pathway occurring naturally in bacteria were elucidated and used to engineer other bacteria and plants, as described in the background of the invention in the application.

PHA copolymers containing 3-hydroxyvalerate (3HV) have been available commercially and have proven useful in a range of applications. These have been produced using bacteria fed appropriate six carbon substrates. In some cases, copolymers with a 3HV level of around 3-12% by weight copolymer are required. In other cases, a 3HV level of 15-30% by weight is more useful. These higher levels are achieved by increasing the level of propionic acid in the feed. However, propionic acid is toxic to the cell, reducing the rate of growth and polymer production, with associated increases in the cost of production, which are significant. Furthermore,

conversion of other co-feed such as 1-propanol or propylene glycol to PHA occurs via propionaldehyde, which may then be converted to propionic acid.

Appellants have discovered a method for overcoming this drawback of propionic acid toxicity, by providing recombinant organisms which not only express the genes necessary for the production of PHA which may include hydroxyhexanoate monomers, but also express a CoA-dependent aldehyde dehydrogenase, which can covert the propionaldehyde intermediate directly to propionyl-CoA. This not only prevents the accumulation of toxic levels of propionic acid in the cells, it also eliminates the need for an additional CoA synthetase or transferase that would have been necessary to convert the propionic acid to the fatty acyl intermediate which is the substrate for PHA synthase.

(ii) Rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 16-23 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Appellants respectfully traverse this rejection.

Claims 16 and 17

Claims 16 and 17 define a recombinant organism selected from the group consisting of bacteria, yeast, fungi and plants for producing polyhydroxyalkanoates, comprising a heterologous gene encoding a Co-A-dependent aldehyde dehydrogenase and a PHA synthase.

As acknowledged by the Examiner (Examiner's Answer, page 13, 3rd paragraph) specification (at least at page 3, lines 9-12 and at least from page 9, line 13 until page 10, line 29)

teaches the **structures** of several representative species of CoA-dependent aldehyde dehydrogenase and several representative species of PHA synthase. Thus the requirement for the description of a representative number of species for a claimed genus has been met, and claims 16 and 17 therefore satisfy the written description requirement. Thus, not only is the Examiner's allegation that the specification discloses solely functional features of the recited genes which are insufficient to be representative of the attributes and features of the entire genus (Examiner's Answer page 11) wrong, it is contradictory to the Examiner's acknowledgement of the disclosure of the structures of several representative species of CoA-dependent aldehyde dehydrogenase and PHA synthase (on page 13 of the Examiner's Answer).

The Examiner alleged that this disclosure of structures of several representative species of the genes encoding the enzymes recited in claim 16 is insufficient to adequately describe the structure of *any* CoA-dependent aldehyde dehydrogenase and *any* PHA synthase having recited functional characteristics which are not representative of the attributes and features of all the members of the genus used to make the claimed microorganism (Examiner's Answer, page 13, 3rd paragraph).

This rejection is wrong for at least two reasons:

First, appellants claim recombinant organisms that include a class of enzymes that by definition shares a common and known function.

Second, appellants have provided a representative number of examples of the claimed enzyme genus, which are predictive of and enabling for the genus.

There is no requirement that an applicant describe "any or all" members of a claimed

genus, only a representative number (MPEP §2163). Appellants have met the requirement by providing a representative number of examples. The standard for a description of any and all genes required by the Examiner is legally incorrect. There is no requirement that an applicant provide so much information that one of ordinary skill must be able to *a priori* identify every member of a claimed genus. "[A]pplicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." See *In re Vaeck*, 947 F.2d 731, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The Examiner also asserted that "**when there is substantial variation within the genus, one must describe sufficient structure and variety of species to reflect the representative structure variation within the genus**" (page 11 of the Examiner's Answer), that the invention is in an unpredictable art, and that "the claimed genus includes species which are widely variant in structure." However, no reasoning or evidence is provided as to why the claimed subject matter is more unpredictable that other areas of genetics, or why the enzymes would be expected to exhibit "substantial variation" relative to each other. A general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description (see MPEP §6163.04). The examiner has provided no evidence in support of the allegation that the same function *can* be provided by many unrelated protein structures such that the genes of the prior art clearly do not put a skilled artisan in possession of all the diversity of protein structures, which will provide the recited function. Even if this was true, it is irrelevant: Appellants are not claiming the proteins, or the genes, which are known, except in the claimed context, which incorporates and expands upon this knowledge.

For at least the reasons set forth above, the Examiner has not met the initial burden of proving that claims 16 and 17 do not meet the written description requirement.

Claims 18-20

Claims 18 states that the organism further comprises one or more genes encoding enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, and acetoacetyl-CoA reductase.

These genes are known in the art, and organisms expressing the genes recited in the claims are also known in the art (*See* Madison). For at least the reasons set forth above with respect to CoA-dependent aldehyde dehydrogenase and PHA synthase, the specification therefore does describe a representative number of species of the enzymes recited in claims 18-20 to satisfy the written description requirement.

However, the Examiner alleged that the claimed invention requires the structures of the genes recited, even though the genes are well known in the art. Appellants again respectfully draw the Examiner's attention to fact that there is no need to recite known structure. See, for example, *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005). However, the Examiner appears to allege at page 15 of the Examiner's Answer that the issues in the instant application are not analogous to *Capon v. Eshhar*, in view of the fact that the genus of products found to lack adequate written description are not the same as those of *Capon v. Eshhar*. If this is indeed the Examiner's reasoning, then all court cases would be non-precedential because the facts are never exactly the same. Moreover, the facts are quite analogous, since the claims in the present application are drawn to genes in an expression system

and the claims in *Capon v. Eshhar* were also drawn to genes (chimeric genes *encoding* a single-chain Fv domain of an antibody and the transmembrane/cytoplasmic/extracellular domains of an endogenous protein). The only difference is that the present claims recite genes encoding full length proteins and in *Capon v. Eshhar*, the genes encode "domains"; however, in both scenarios, the genes are known in the art and therefore, recitation of known structure is not required.

Therefore, claims 18, 19 and 20 meet the written description requirement.

Claim 21

The Examiner acknowledged that the specification fulfils the written description requirement with respect to the CoA-dependent aldehyde dehydrogenase, but not with respect to the genus of PHA synthase genes. It should be noted that genes encoding PHA synthase genes from multiple sources have been disclosed, and patented, since 1987, as evidenced by the many patents and publications provided by Appellants in their Information Disclosure Statements and art cited in the application. It is particularly significant that all of these including those that are divergent in structure, were isolated using probes derived from other PHA synthase genes, including those with different substrate specificity.

Appellants submit that for the forgoing reasons and at least the reasons set forth for claims 16 and 17 with respect to the PHA synthase gene, claim 21 meets the written description requirement.

Claim 22

Claim 22 specifies that the recombinant organism is a bacteria. Bacteria suitable for

production of PHAs are well known to those of skill in the art and are described in the specification at least from page 1, line 10, until page 3, line 8 (*See* also, Madison, and numerous patents and publications cited by Appellants in their application and references cited in Information Disclosure Statements).

Appellants submit that for at least the reasons set forth for claims 16 and 17 with respect to the CoA-dependent and PHA synthase genes, claim 21 meets the written description requirement.

Claim 23

Claim 23 specifies that the recombinant organism is a plant. Plants suitable for production of PHAs are well known to those of skill in the art (*See* for example, Madison and issued patents claiming priority to 1989 and 1991, cited in the Information Disclosure Statements). These demonstrate that PHAs have been produced in a wide range of plants.

Appellants submit that for at least the reasons set forth for claims 16 and 17 with respect to the CoA-dependent and PHA synthase genes, claim 21 meets the written description requirement.

(iii) Rejection under 35 U.S.C. § 112, first paragraph, enablement

Claims 16-23 were rejected under 35 U.S.C. § 112, first paragraph, as not enabled. Appellants respectfully traverse this rejection.

Claims 16 and 17

Applicants respectfully submit that from the guidance provided in the specification coupled with knowledge in the art, one of ordinary skill in the art would be able to make and use

the claimed organisms without undue experimentation. Furthermore, the state of the knowledge in the art is very high, and the field is not especially unpredictable as of the filing date of this application.

The Examiner's sole argument stated in different variations is that the specification does not provide "any and all" genes required to make the claimed organisms. Furthermore, the Examiner appears to assume that in order to locate other genes appropriate for use in theclaimed organisms, one would begin with a universe of infinitely variable and random polynucleotides, and from that point of view, the specification fails to enable one to choose appropriate polynucleotides from that universe. However, this is not a realistic strategy that any person in the biotechnology field would ever employ, and if this is the reasoning on which the rejection is based, it must be withdrawn because it is based on a false and unfounded assumption of a unreasonably low level of skill in the art.

As discussed above, genes recited in claims 16 and 17 are known in the art and are disclosed in the specification (see page 3, lines 9-12, page 9, line 13 until page 10, line 29). Methods for heterologous expression in all of the organisms recited in claim 16 are known in the art (See Madison, Huisman, or Poirier, et al., *Appl. Environ. Microbiol.* 67(11):5254-60 (2001) ("Poirier", a copy of which was attached to the Appeal Brief)). The art is very well developed in regard to the process of expressing the genes recited in the claims (albeit not in the same combination), in the heterologous systems recited in claim 16 (See for example Peoples and U.S. Patent No. 6,329,183 to Skraly, et al., cited in the information disclosure statement filed on Dec, 23, 2003, and considered by the Examiner on June 15, 2006 and U.S. Patent No. 5,534,432 to

Peoples et al. ("Peoples" cited in the information disclosure statement filed on Dec, 23, 2003, and considered by the Examiner on June 15, 2006). Thus, one of skill in the art can readily extrapolate from the actual examples in the application to other aldehyde dehydrogenase, acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase and PHA synthase genes from other sources that are known in the art as evidenced by disclosure in the specification and literature cited and enclosed in this appeal brief. Thus from the direction given in the specification and knowledge in the art, one skilled in the art can readily make and use the claimed organisms without undue experimentation.

The Examiner alleged that the specification does not provide enablement for "any or all PHA synthase" and "any or all fatty acid:acyl CoA transferase" isolated from "any or all source, including any or all mutants, recombinants or variants thereof" (Examiner's Answer, pages 19-20). The Examiner further alleged that undue experimentation would be required to practice the invention, but advanced no evidence or reasoning why such would be the case, beyond the unfounded assertion that "[t]he scope of the claims is not commensurate with the enablement provided by the disclosure" (Examiner's Answer, paragraph bridging pages 17 and 18). This is stated to be due to the "extremely large number of polynucleotide encoding polypeptides of virtually any structure." However, no evidence or reasoning is provided as to why one of ordinary skill would ever believe that there would be an "extremely large number" of polynucleotides that can be used in the invention, or that appropriate polynucleotides would encompass "any structure". The references provided by the Examiner in support of the fact that single mutations/small amino acid changes *can* change protein function is not evidence that there

is an unlimited number of genes encoding CoA-dependent aldehyde dehydrogenases and PHA synthases that can be used to make the claimed organisms.

If the Examiner is assuming that the "very large number" is every possible polynucleotide of every possible sequence, then this reasoning is flawed and not a valid basis for the rejection. The claims require that the polynucleotides encode a PHA synthase and a CoA-dependent aldehyde dehydrogense. The vast majority of polynucleotides of random sequences will not encode either of these enzymes, and a person of ordinary skill in the art understands this. No practitioner in the biotechnological arts would, or ever has, started with random polynucleotides to obtain a polynucleotide encoding a particular enzyme. Instead, one of ordinary skill would begin with a known sequence, and use it to search databases for other sequences which likely encode another version of the enzyme. It was for precisely this reason that applicants provided sequences for a PHA synthase and a coA-dependent aldehyde dehydrogenase – so that practitioners could use these sequences as guides to obtain additional PHA synthase and CoA-aldehyde dehydrogenase genes. In fact, the Examiner clearly states on page 22 of the Examiner's Answer that it is not routine in the art to test an infinite number of proteins to determine which ones have the desired activity, and that instead, on of skill in the art would have some knowledge or guidance as to which proteins are more likely to display the desired activity so that the amount of screening is limited. Appellants have provided a representative number of genes which would be expected to encode the recited enzymes. Thus it is unclear what the Examiner's requirement with respect to "any and all genes" or "known and unknown genes" is. This is neither the standard nor common practice in the art.

If the basis for the rejection is that one of ordinary skill is unable to use one sequence as a guide to obtain other sequences appropriate for use in the invention, then evidence of this must be provided - especially since Appellants have provided an abundance of evidence to the contrary, in their specification and references cited therein and in the Information Disclosure Statements. Without such evidence, the Examiner has assumed that the level of skill in the art is artificially and inappropriately low. If the basis of the rejection is that one would find other genes by testing random polynucleotides, then evidence must be provided that this is a commonly-used strategy in the art.

The Examiner appears to require that one should be able to predict which polynucleotides will have the desired activity before they are isolated or tested. However, in *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988), for example, it could not have been predicted *a priori* which hybridomas of those made would be active, and the court explicitly held that some experimentation can still be required for an enabling disclosure. Absolute predictability of the activity of embodiments which may be embraced within the claims is not a requirement of the statute. The decision in *In re Angstadt* 190 U.S.P.Q. 218 (C.C.P.A. 1976) clearly states that every embodiment need not be disclosed, even in an unpredictable art, and clearly permits the presence of a screening step to identify those embodiments which possess the desired activity. In *Angstadt*, the Court specifically dismissed the notion that the specification must provide a level of guidance that would predict the outcome of an experiment (or reaction) "with reasonable certainty before performing the reaction" and that "such a

proposition is contrary to the basic policy of the Patent Act, which is to encourage disclosure of inventions and thereby to promote progress in the useful arts."

It is well settled that some experimentation is permitted under 35 U.S.C. § 112, first paragraph. Thus, the present specification enables the claimed invention and claims 16 and 17 are enabled.

Claims 18-20

For at least the reasons set forth with respect to claims 16 and 17 and below, claims 18-20 are enabled. The genes recited in the claims are known in the art, and organisms expressing the genes recited in the claims are also known in the art (*See* Madison). Furthermore, Examples 3-7 describes the production of PHA containing hydroxyvalerate, wherein the organism expresses the genes recited in claim 18. Therefore, claims 18-20 are enabled.

Claim 21

For at least the reasons set forth with respect to claims 16 and 17 and below, claim 21 is enabled. Claim 21 recites all of the limitations of claim 16 and further defines the CoA-dependent aldehyde dehydrogenase to be the *eut*E of *E coli*. The specification teaches how to make recombinant organisms expressing *eut*E form *E. coli* (from page 16-18, and Examples 4 and 5). Therefore, claim 21 is enabled.

Claim 22

For at least the reasons set forth with respect to claims 16 and 17 and below, claim 22 is enabled. Claims 22 recites all of the limitations of claim 16, and further defines the organism as a bacteria. Bacteria suitable for production of PHAs are well known to those of skill in the art (*See*

Madison, pages 37-40 and 41-44). Examples 3-7 describes the production of PHA containing hydroxyvalerate in *E. coli*. Therefore claim 22 is enabled.

Claim 23

For at least the reasons set forth with respect to claims 16 and 17 and below, claim 23 is enabled. Claim 23 recites all of the limitations of claim 16, and further defines the organism as a plant. Plants that can be used for the production of PHA are known in the art. (See Madison, page 45 and Poirier). The genes recited in the claims to be heterologously expressed in the plants are not only known in the art, they are disclosed in the specification. Thus, it would be easy for one of ordinary skill in the art, using knowledge in the art and Appellants discovery of the requisite combination of genes necessary to avoid accumulation of propionic acid in the cytosol, to make the claimed organisms. Therefore, claims 23 is enabled.

Conclusion

The genes needed to make the claimed organisms are known. Methods for heterologous expression are known in the art, and the specification provides numerous examples. There is no requirement for disclosure of any and every gene that could possibly be used in order to satisfy the enablement or written description requirements. The Examiner has not established a *prima facie* case of non-enablement or a lack of written description. From the disclosure in the specification and what is known in the art, claims 16-23 clearly meet the written description and enablement requirements.

For the foregoing reasons, Appellants submits that claims 16-23 are patentable.

Respectfully submitted,

/Patrea L. Pabst/
Patrea L. Pabst
Reg. No. 31,284

Date: February 15, 2008

PABST PATENT GROUP LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, Georgia 30361
(404) 879-2151
(404) 879-2160 (Facsimile)